Hepatitis B virus infection and risk of coronary artery disease: a meta-analysis

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Background: Hepatitis B virus (HBV)-infected patients might be associated with coronary artery disease (CAD) from process of chronic inflammation. However, available studies yield conflicting results. This meta-analysis was performed to assess risk of CAD in HBV-infected patients.

Methods: We searched MEDLINE and EMBASE for relevant literatures from database inception to June 2016. Studies comparing the risk of CAD among HBV-infected patients versus subjects without HBV infection using hazard ratio (HR), odd ratios, or relative risk (RR) were included. Random-effect model and generic inverse variance method were used to combine odds ratio (OR) and 95% confidence interval (CI).

Results: A total of five studies, including three cross-sectional studies, one case-control study, and one cohort study, were subjected to analysis. The result demonstrates no significant risk of CAD among chronic HBV-infected patients and subjects without HBV infection (OR, 0.68; 95% CI, 0.40–1.13).

Conclusions: This meta-analysis did not demonstrate a significantly increased risk of CAD among HBV-infected patients.

Keywords: Hepatitis B virus (HBV); coronary artery disease (CAD); myocardial infarction; heart attack; meta-analysis

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Introduction

Coronary artery disease (CAD) raises health concerns as the major cause of sudden death in the United States. It affects more than 17.8 million American in 2010 (1). Risk factors of CAD include age, male sex, smoking, diabetes mellitus, hypercholesterolemia and hypertension (2). More recently, it has been demonstrated that chronic inflammatory state associated with chronic infection and chronic autoimmune disease, such as chronic hepatitis C virus (HCV) infection, rheumatoid arthritis and inflammatory myositis, could also be an independent risk factor for CAD (3-6).

Chronic hepatitis B virus (HBV) infection is one of the most common chronic infections affecting approximately 2.8 billion patients worldwide (7). In consideration of chronic inflammation, chronic HBV-infected patients might have a higher possibility of developing CAD. However, data on the relationship between HBV and CAD remains inconclusive as studies have yielded conflicting results (8-12). This systematic review and meta-analysis was conducted to summarize all available evidence to assess the risk of CAD among HBV-infected patients.

Methods

Search strategy

Published studies were retrieved independently by two authors (Karn Wijarnpreecha and Patompong Ungprasert) from MEDLINE and EMBASE database for available literatures up to June 2016. Electronic search strategy was performed by integrating the terms for "hepatitis B virus" in conjunction with the term "coronary artery disease". Additional data is described in *Table S1*. Non-English publications were included. Further evaluation for potential relevant studies was performed manually on bibliography of selected searched articles.

Inclusion criteria

We included studies that met the following inclusion criteria: (I) observational studies (case-control, cross-sectional or cohort studies) published as original articles to determine the risk of CAD among HBV-infected patients compared with subjects without HBV infection; (II) detailed odds ratio (OR), relative risk (RR), hazard ratio (HR) or standardized incidence ratio (SIR) with 95% confidence interval (CI) were given. If the ratios were not available, the study must provide adequate calculable raw data.

Retrieved studies were independently reviewed for their eligibility by three authors (Karn Wijarnpreecha, Charat Thongprayoon and Patompong Ungprasert). Mutual agreement was used to solve controversy. For nonrandomized studies, Newcastle-Ottawa scale (13) was used to further appraise the publications in three areas including study selection, study comparison, and determination of the exposure for case-control study and outcome of interest for cohort study. For cross-sectional study, we classified each study by using adapted form of the Newcastle-Ottawa scale (14). The quality appraisal process was conducted by Karn Wijarnpreecha, Charat Thongprayoon and Patompong Ungprasert.

Data extraction

We obtained the following data from each article by using a standardized data collection form: last name of the first author's, name of the study, year of publication, place where the study was conducted, number of subjects, demographics of subjects, diagnostic method of HBV infection, definition of CAD, diagnostic method of CAD, adjusted effect estimates with 95% CI and covariates that were adjusted in the multivariate analysis. To avoid errors, studies were assessed by the three authors independently. Data collection from for each study was cross-checked and was reported back to the original studies for data inconsistency.

Statistical analysis

For data analysis, we used Review Manager 5.3 software from the Cochrane Collaboration (London, UK). Pooled estimates and their standard errors from each study were analyzed by using generic inverse variance method as described by DerSimonian and Laird, which weighted each study according to its standard errors (15). For uncommon of outcome of interest, we used RR of cohort study as an estimate for OR to combine with OR from cross-sectional and case-control study. Since this meta-analysis combined data from three different study designs, we expected that between-study heterogeneity could be high and decided to use random-effect model, rather than fixed-effect model. Between-study heterogeneity was assessed by Cochran's Q test which is complimented by I^2 statistic. A value of I^2 of 0–25% represents insignificant heterogeneity, 26–50% represents low heterogeneity, 51–75% represents moderate heterogeneity, and more than 75% represents high heterogeneity (16).

Results

Of the 1,372 potential studies identified using our search strategy, 522 studies were from Medline and 850 studies were from EMBASE. We reviewed titles and abstracts of 909 studies after excluded 463 studies because of their repetition. A total of 881 studies were excluded at this stage since they were case reports, letters to editor, review articles, *in vitro* studies, animal studies or interventional studies. Twenty-eight studies underwent full-text article assessed for eligibility. Eighteen of them were excluded for absence of interest outcome while five studies were excluded since they were observational studies without comparison available. Therefore, a total of five studies, including three cross-sectional studies, one case-control study, and one cohort study, met the eligibility criteria and were subjected to analysis (8-12). Detailed literature retrieval, review and selection process are shown in *Figure 1*. Study characteristics and quality assessment are listed in *Table 1*. Preferred reporting Items for Systematic Reviews and

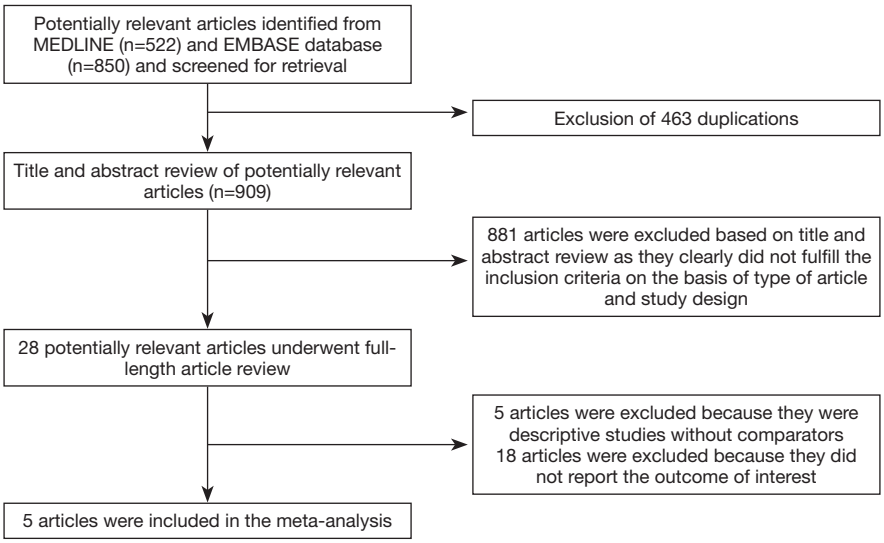

Figure 1 Literature review process.

Meta-Analysis (PRISMA) is provided as *Table S2* (17). The inter-rater agreement for the quality assessment using the Newcastle-Ottawa scale was high with the kappa statistics of 0.88.

We found no significant association between HBV infection and risk of CAD with the pooled OR of 0.68 (95% CI, 0.40–1.13). There was moderate statistical heterogeneity between studies with an I^2 of 64%. *Figure 2* illustrated forest plot of this meta-analysis.

Evaluation for publication bias

Funnel plot to evaluate publication bias is shown in *Figure 3*. The graph is fairly symmetric and provides no suggestion of publication bias.

Discussion

The association between chronic inflammation and accelerated atherosclerosis has long been recognized. In fact, studies have demonstrated an excess risk of CAD among HCV-infected patients compared with subjects without HCV infection (3,18). However, in this meta-analysis, we did not find a significant association between risk of CAD and HBV infection patients.

The reason behind the lack of association is unclear. It is possible that the inflammatory burden of chronic HBV infection is relatively low. In fact, a study has demonstrated that mean C-reactive protein levels among HBV-infected patients was not higher than HBV-seronegative individuals (8,9,12).

In contrast to studies on HCV infection that found an increased frequency of metabolic disturbance (19,20), studies of HBV-infected patients did not observed an increased prevalence of traditional risk factors of CAD including diabetes, hypertension, and hyperlipidemia (9). The absence of metabolic complication could be another factor for the lack of increased CAD risk among these patients.

Although most of the included studies were of high quality as reflected by the high quality assessment scores, we acknowledged that this meta-analysis had some limitations. Therefore, the results should be interpreted with caution.

First, the primary studies included in this meta-analysis were conducted primarily in Asia. Therefore, the results might not be generalizable to other populations with different baseline cardiovascular risk. Second, the heterogeneity was not low in this study. Third, most of the included studies did not adjust their effect estimates for several known risk factors for CAD such as diabetes, hyperlipidemia, and hypertension. Moreover, most of the included studies were cross-sectional in nature. Therefore, temporal relationship between HBV and CAD could not be established.

In summary, this meta-analysis did not demonstrate a significantly increased risk of CAD among HBV-infected patients.

Table 1 Main characteristics of the studies in the meta-analysis

Studies	Amirzadegan *et al*. (8)	Ghotaslou *et al*. (9)	Momiyama *et al*. (10)	Sung *et al*. (11)	Tong *et al*. (12)
Country	Iran	Iran	Japan	South Korea	China
Study design	Cross-sectional	Cross-sectional	Case-control	Cohort	Cross-sectional
Year	2007	2008	2005	2007	2005
Number of participants	830	5,004	630	521,421	434
Participants	Subjects who underwent coronary angiography due to chest pain at Tehran Heart Center, Tehran, Iran, were consecutively recruited	Subjects who underwent coronary angiography due to chest pain at Madani Heart Hospital, Tabriz, Iran, were consecutively recruited	Subjects with CAD and age- and sex-matched controls without CAD were identified from coronary angiography database of the study hospital	Korean male public servants aged 30 to 64 years who underwent a health examination provided by the KNHS between 1986 and 1990	Subjects who underwent coronary angiography at Zhongshan Hospital, Shanghai, China, were consecutively recruited
Mean age of participants in years	57.0	57.7	Case: 64.0; control: 64.0	Case: 40.6; comparator: 41.5	62.2
Percentage of female	36.3	30.5	Case: 18.0; control: 18.0	0	29.0
Method used to diagnose HBV infection	Positive HBsAg (by ELISA)	Positive HBsAg (by ELISA)	Positive HBsAg (by ELISA)	Positive HBsAg (by ELISA or reverse hemagglutination)	Positive HBsAg (by ELISA)
Method used to diagnose CAD	Angiography (≥50% stenosis of ≥1 coronary artery)	Angiography (≥50% stenosis of ≥1 coronary artery)	Angiography (≥50% stenosis of ≥1 coronary artery)	ICD-10 codes of CAD: (I21–I24)	Angiography (≥50% stenosis of ≥1 coronary artery)
Confounders that were adjusted	None	None	None	Age, BMI, height, serum glucose, hypertension categories, lipid categories, ethanol consumption, smoking, physical activity, monthly pay level, area of residence	None
Quality assessment (Newcastle-Ottawa scale)	Selection: 2; comparability: 1; outcome: 2	Selection: 3; comparability: 1; outcome: 3	Selection: 2; comparability: 1; outcome: 2	Selection: 3; comparability: 2; outcome: 3	Selection: 2; comparability: 1; outcome: 2

CAD, coronary artery disease; KNHS, Korean National Health System study; HBV, hepatitis B virus; HBsAg, hepatitis B surface antigen; ELISA, enzyme-linked immunosorbent assay; ICD-10, International Classification of Disease 10; BMI, body mass index.

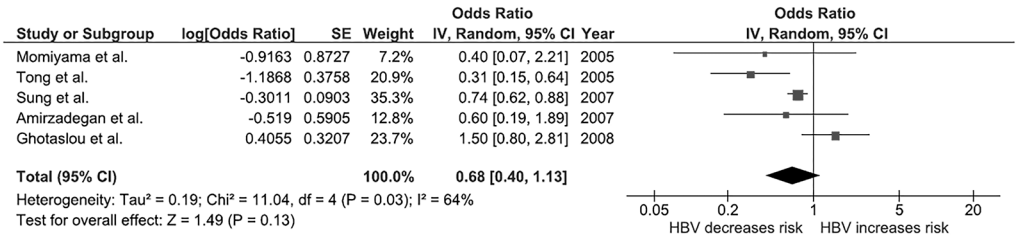

Figure 2 Forest plot of the complete analysis.

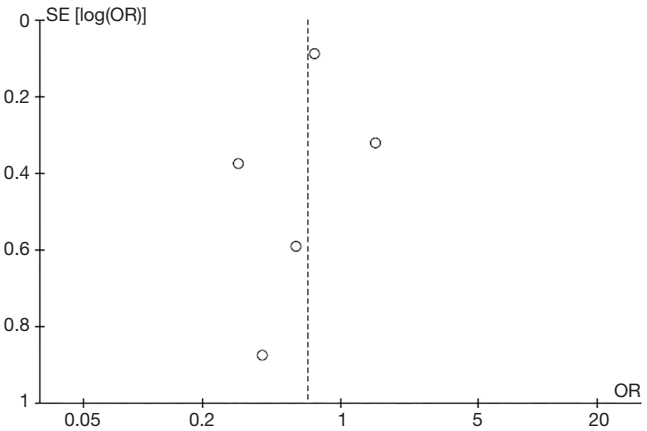

Figure 3 Funnel plot. OR, odds ratio.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Supplementary

Table S1 Search strategy

Database: Ovid MEDLINE

1. Hepatitis B.mp. or exp hepatitis B/
2. Exp hepatitis B virus/
3. HBV.mp.
4. Hepatitis B surface antigens.mp. or exp hepatitis B surface antigens/
5. HBsAg.mp.
6. Or/1–5
7. Exp coronary artery disease/
8. Coronary artery atherosclerosis.mp.
9. Coronary artery obstruction.mp.
10. Exp coronary disease/
11. Exp acute coronary syndrome/
12. Exp myocardial infarction/
13. Exp coronary thrombosis/
14. Exp angina pectoris/
15. Exp angina, unstable/
16. Or/7–15
17. 6 and 16

Database: EMBASE

1. Hepatitis B.mp. or exp hepatitis B/
2. Hepatitis B virus.mp. or exp hepatitis B virus/
3. HBV.mp.
4. Hepatitis B surface antigen.mp. or exp hepatitis B surface antigen/
5. HBsAg.mp.
6. Or/1–5
7. Exp coronary artery disease/
8. Exp coronary artery atherosclerosis/
9. Exp coronary artery obstruction/
10. Exp coronary atherosclerosis/
11. Exp heart muscle ischemia/
12. Exp heart infarction/
13. Exp coronary artery thrombosis/
14. Exp angina pectoris/
15. Exp unstable angina pectoris/
16. Or/7–15
17. 6 and 16

Table S2 Preferred reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) 2009 checklist

Section/topic	#	Checklist item	Reported on page #
Title	1	Identify the report as a systematic review, meta-analysis, or both	1
Abstract			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number	1
Introduction			
Rationale	3	Describe the rationale for the review in the context of what is already known	1
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS)	1
Methods			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., web address), and, if available, provide registration information including registration number	2
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale	2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched	2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated	2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis)	2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators	2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made	2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis	*Table 1*
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means)	2
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis	2
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies)	2
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified	2
Results			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram	2
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations	*Table 1*
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12)	*Table 1*
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (I) simple summary data for each intervention group; (II) effect estimates and confidence intervals, ideally with a forest plot	*Figure 2*
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency	3
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15)	3
Additional analysis	23	Give results of additional analyses, if done [e.g., sensitivity or subgroup analyses, meta-regression (see item 16)]	3
Discussion			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers)	4
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias)	4
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research	4
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review	5